Precision Psychiatry for Depression and Anxiety: Using Biotypes to Personalize Treatment Selection

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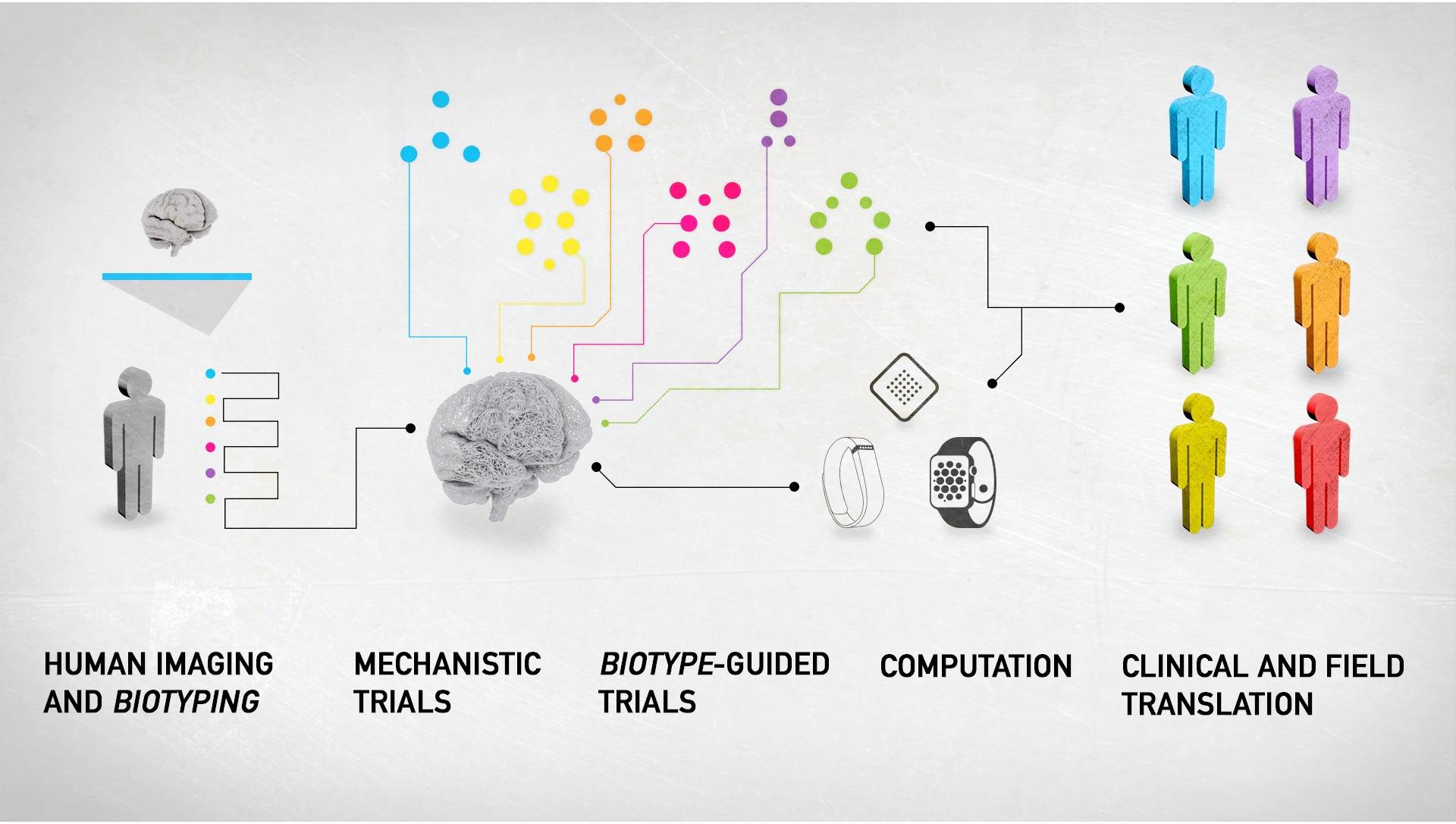
PMHW
Stanford Center for Precision Mental Health and Wellness



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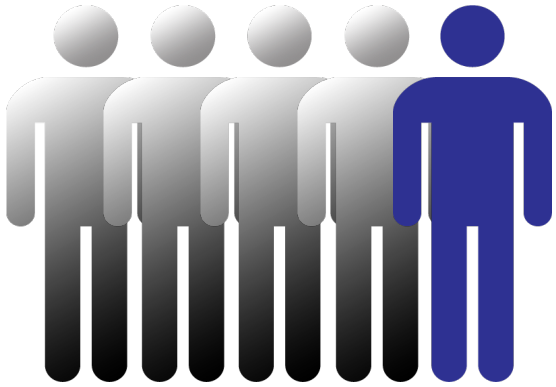

1 IN 5

PANDEMIC-RELATED INCREASE IN RATES OF DEPRESSION & ANXIETY

2 in 5

https://www.cdc.gov/mmwr/volumes/70/wr/mm7013e2.htm

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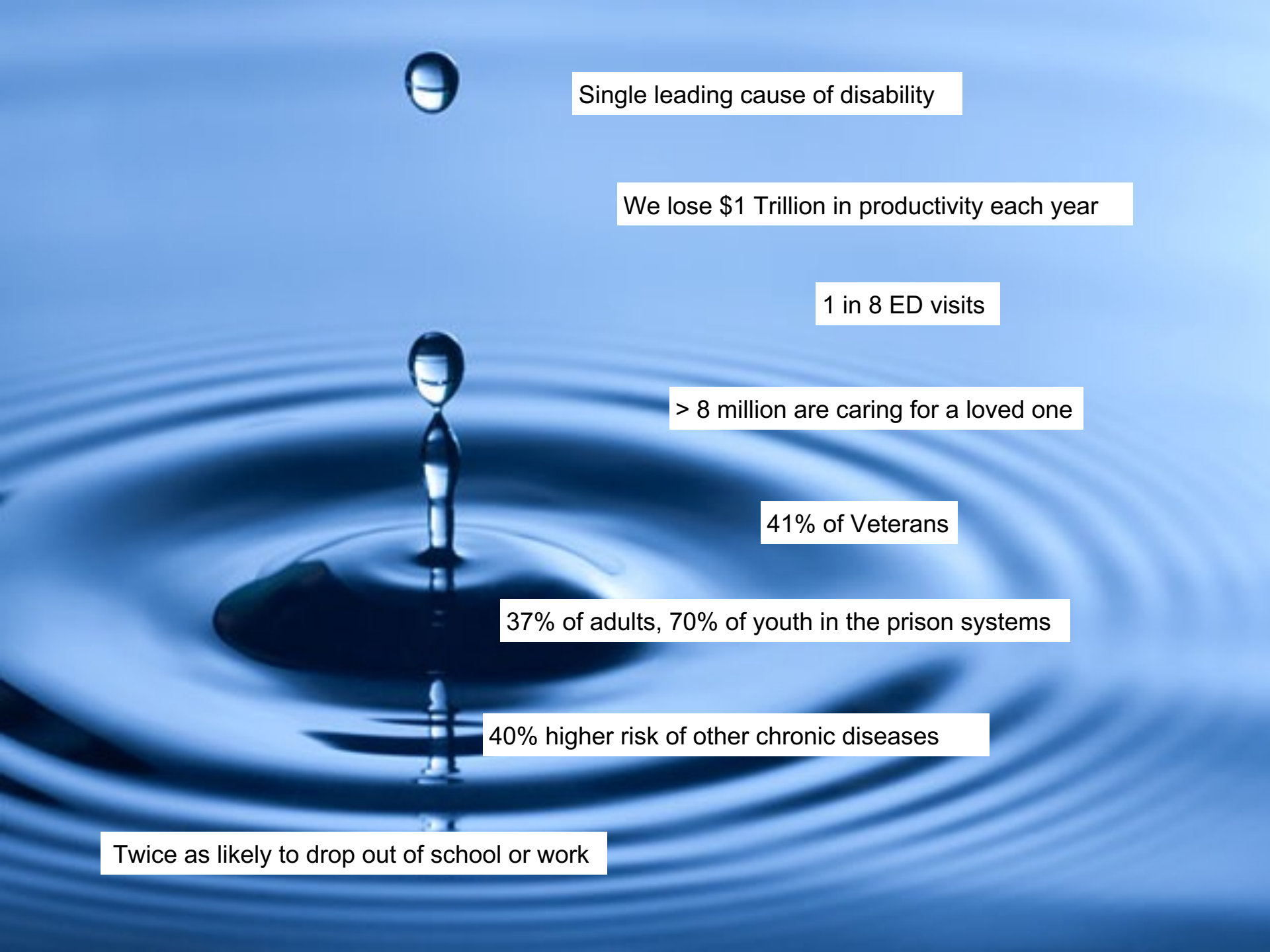
Single leading cause of disability
We lose $1 Trillion in productivity each year
1 in 8 ED visits
> 8 million are caring for a loved one
41% of Veterans
37% of adults, 70% of youth in the prison systems
40% higher risk of other chronic diseases
Twice as likely to drop out of school or work

Every 40 seconds, someone dies by suicide

World Health Organization

IN THE LAB

Can precision medicine do for depression what it's done for cancer? It won't be easy

By MEGAN THIELKING @meggophone / MAY 9, 2018

HYACINTH EMPINADO/STAT

At a growing number of research centers across the country, scientists are scanning brains of patients with depression, drawing their blood, asking about their symptoms, and then scouring that data for patterns. The goal: pinpoint subtypes of depression, then figure out which treatments have the best chance of success for each particular variant of the disease.

The idea of precision medicine for depression is quickly gaining ground — just last month, Stanford announced it is establishing a Center for Precision Mental Health and Wellness.

https://www.statnews.com/2018/05/09/precision-medicine-depression-treatment/

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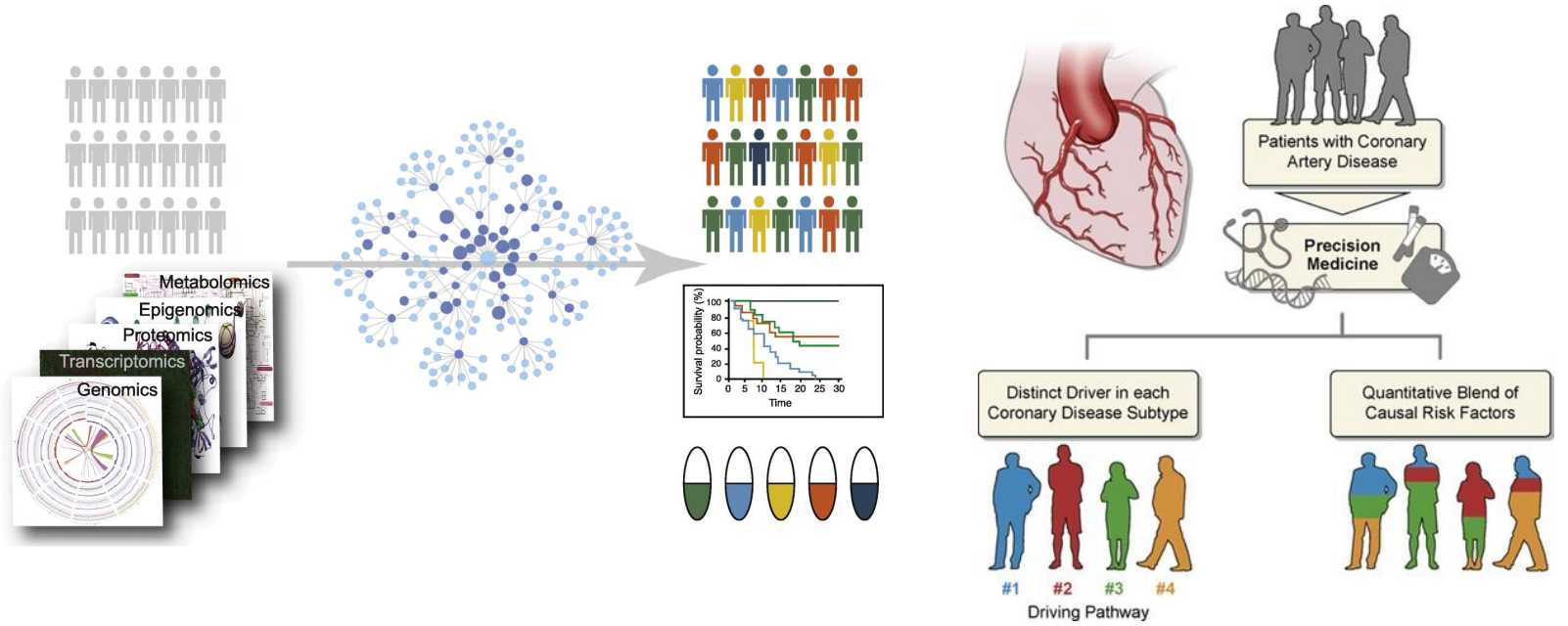
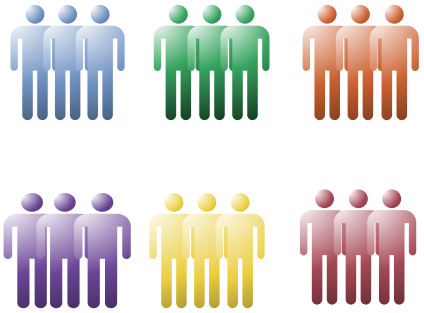

Metabolomics
Epigenomics
Proteomics
Transcriptomics
Genomics
Survival probability (%)
100
80
60
40
20
0
0 5 10 15 20 25 30
Time
Patients with Coronary Artery Disease
Precision Medicine
Distinct Driver in each Coronary Disease Subtype
Quantitative Blend of Causal Risk Factors
#1 #2 #3 #4
Driving Pathway



- Self-Report
- Genes
- **Brain circuits**
- Physiology
- Behavior

Williams Lancet Psychiatry 2016. Depression and Anxiety 2017.

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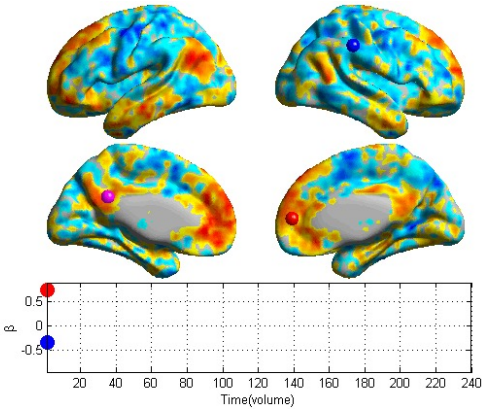
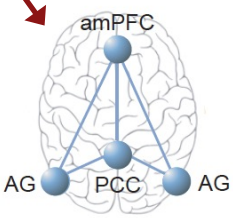
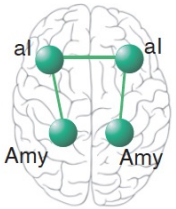
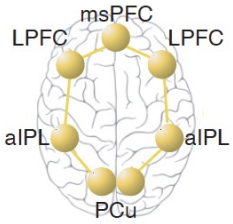
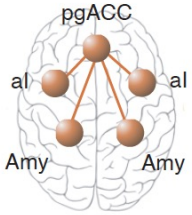
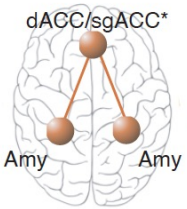
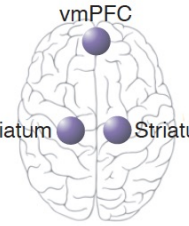
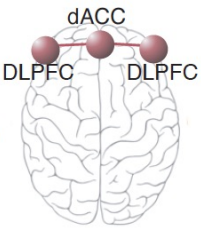
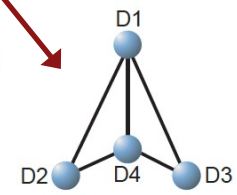
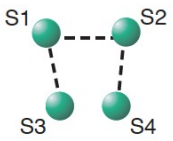
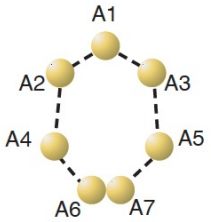
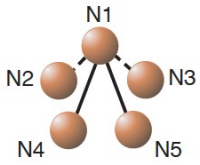
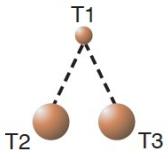
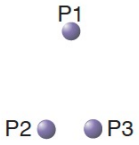
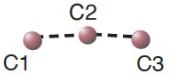


Development and testing of a standardized pipeline suited to biotype trials

Circuit	Default Mode	Salience	Attention	Negative Affect - Sad	Negative Affect - Threat	Positive Affect	Cognitive Control
Standardizing Regions & Connections							
Quantifying Regional Circuit Clinical Scores							
Computing Global Circuit Clinical Scores	$(C_{D1,D2} + C_{D1,D3} + C_{D1,D4} + C_{D2,D4} + C_{D3,D4})/5$	$(-C_{S1,S3} - C_{S2,S4} - C_{S1,S2})/3$	$(-C_{A1,A2} - C_{A1,A3} - C_{A2,A4} - C_{A3,A5} - C_{A4,A6} - C_{A5,A7})/6$	$(A_{N1} + A_{N2} + A_{N3} + A_{N4} + A_{N5} - C_{N1,N2} - C_{N1,N3} + C_{N1,N4} + C_{N1,N5})/9$	$(-A_{T1} + A_{T2} + A_{T3} - C_{T1,T2} - C_{T1,T3})/5$	$(-A_{P1} - A_{P2} - A_{P3})/3$	$(-A_{C1} - A_{C2} - A_{C3} - C_{C1,C2} - C_{C2,C3})/5$

Goldstein, Ball … Williams. Biological Psychiatry, 2021

Patents 62/589,452 & 15/820, 338. Systems & Methods for Detecting Complex Networks in MRI Image Data

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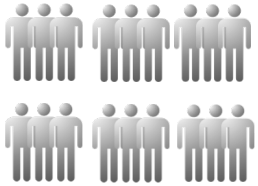
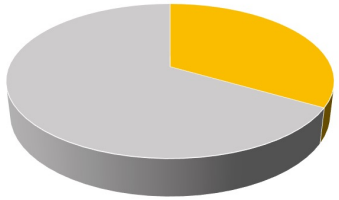
Now



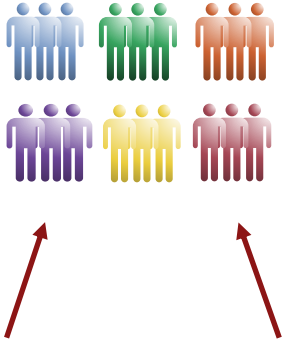
Expertise &
dedication

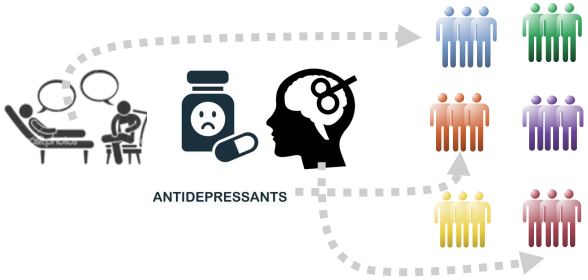
Try one,
Wait and see.
Try another

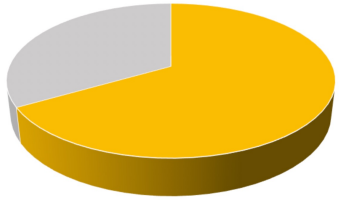


1/3
get better first try

Future







At least double

Accuracy from trials undertaken so far is 75-81%

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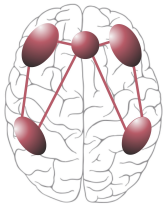
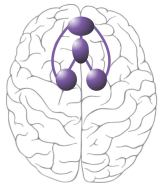
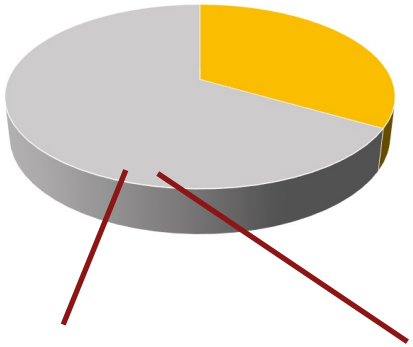
Cognitive impairment

Anhedonia



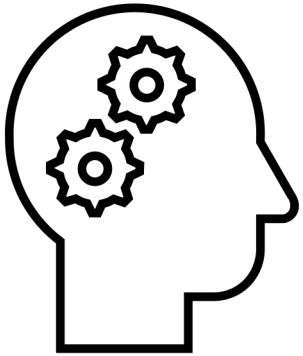




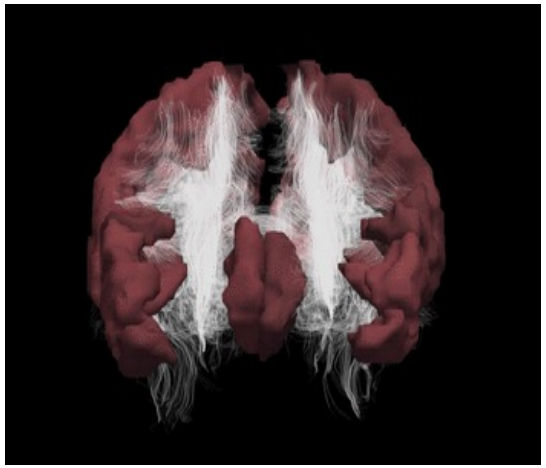
More likely non-responders

Poorer function, higher suicide risk

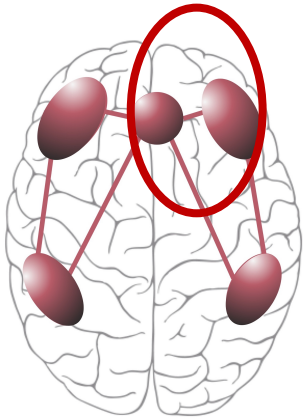
Williams Lancet Psychiatry 2016. Depression and Anxiety 2017; Trostheim et al. JAMA Network Open (2020); Chakrabarty et al. Focus (2016); Conradi et al. Psychol Med (2011).



Cognitive impairments



Cognitive control circuit



Dorsal Lateral Prefrontal Cortex (DLPFC)

‘First line’ antidepressants

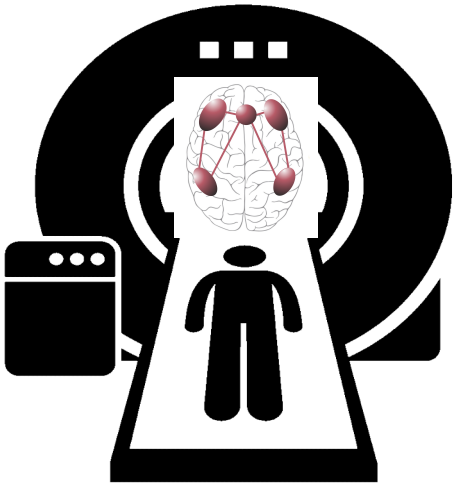
Williams et al. Trials 2011, 12:4
http://www.trialsjournal.com/content/12/1/4

TRIALS

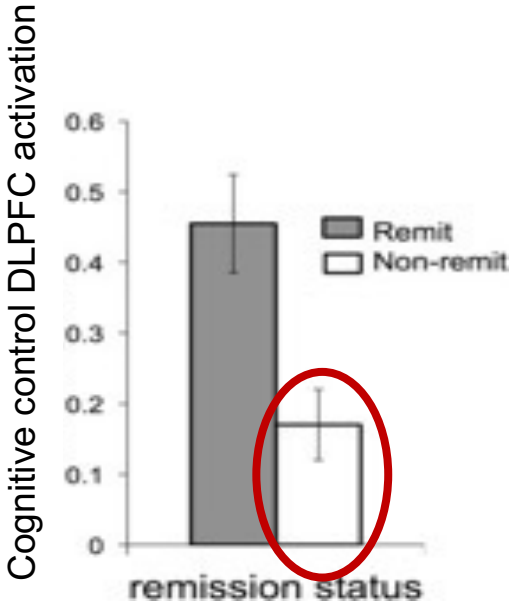
STUDY PROTOCOL Open Access

International Study to Predict Optimized Treatment for Depression (iSPOT-D), a randomized clinical trial: rationale and protocol

Leanne M Williams[1,2*], A John Rush[3], Stephen H Koslow[1,4], Stephen R Wisniewski[5], Nicholas J Cooper[6], Charles B Nemeroff[7], Alan F Schatzberg[8], Evian Gordon[2,6]



Escitalopram (Lexapro)
Sertraline (Zoloft)
Venlafaxine (Effexor)



Baseline → 8 weeks treatment → Outcomes assessed

Gyurak et al., Biological Psychiatry (2016); Tozzi et al., Biological Psychiatry (2020)

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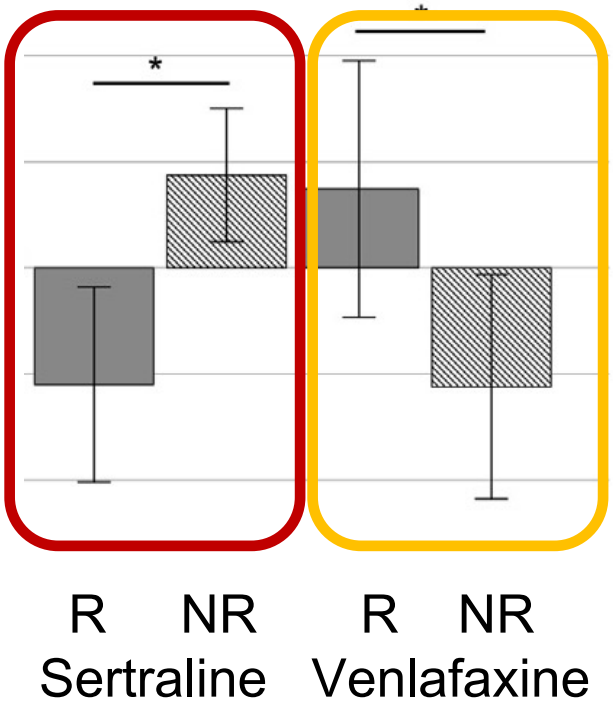
Cognitive control circuit connectivity differentiated response to different types of antidepressant



Tozzi et al., Biological Psychiatry, 2020; editorial Fu (2020), Biological Psychiatry

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Behavioral therapy focused on cognitive problem solving

SOBC | Science Of Behavior Change

NIH Grants

- UH2 HL132368
- UH3 HL132368
- R01 HL119453

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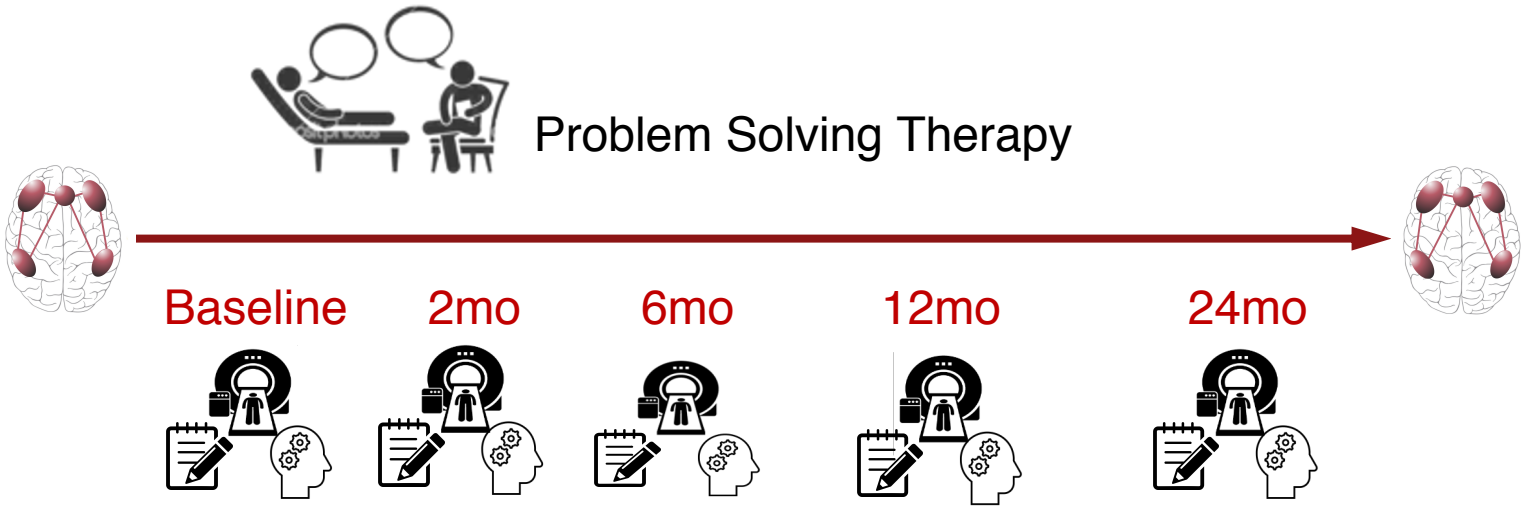
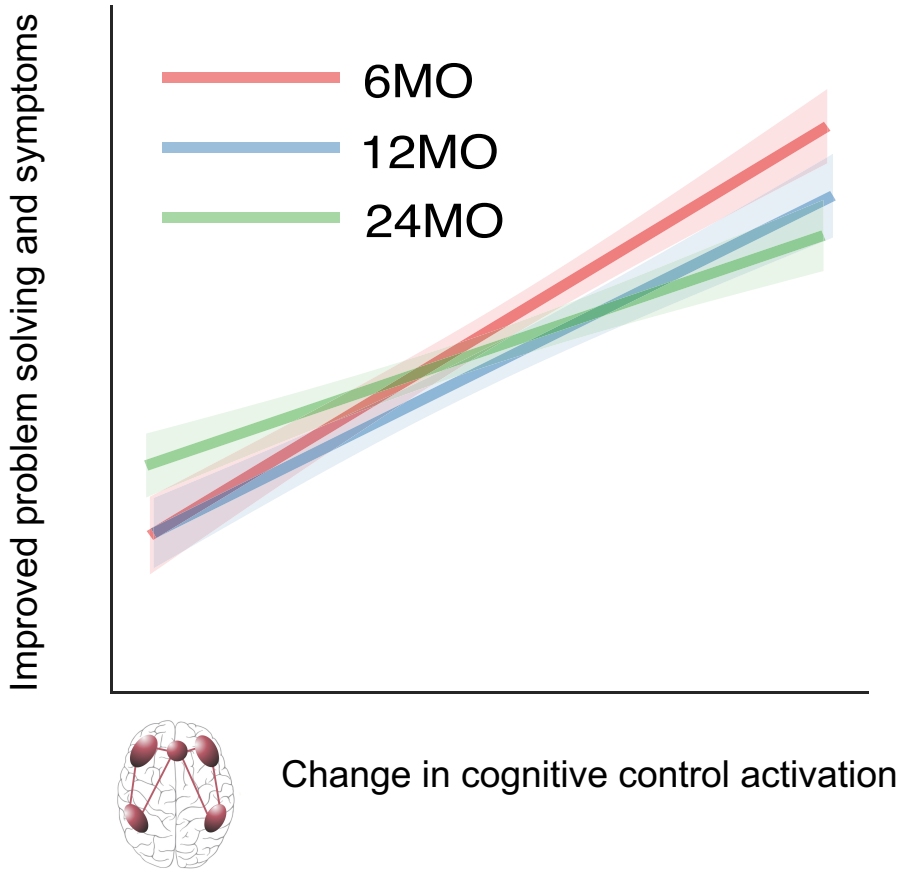


Williams et al. Behavior Research and Therapy (2018); Ma et al JAMA (2019)

NIH Grants: UH2 HL132368 , UH3 HL132368, R01 HL119453

Cognitive control circuit activation increased with therapy. This increase predicted improvements 6, 12 and 24 months later



Zhang X et al., Biological Psychiatry (2021)

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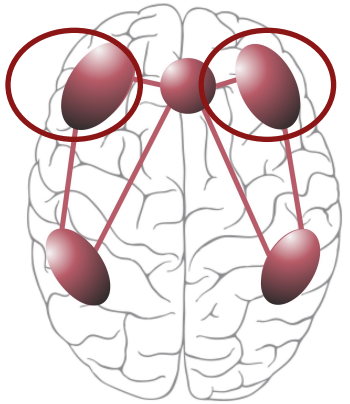
Targeted novel treatments

Targeting cognitive control with guanfacine

- Guanfacine-immediate release
- Selective for α_2 receptors → strengthen prefrontal connections
- Shown to increase DLPFC activation
- Shown to improve cognition
- Meets safety/availability criteria



e.g., McAllister et al. Int J Psychophysiol (2011); Arnsten et al. Science (1985); Jarrott et al. Br J Pharmacol (1982); Kim et al. Psychopharmacol (2012).

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Guanfacine: Ms. A's Case

- 52 yo female
- "*I haven't been able to concentrate on work for a month now. I haven't put out anything productive…I find myself be easily distracted*."
- Guanfacine 1 mg daily for one week, then 2 mg daily

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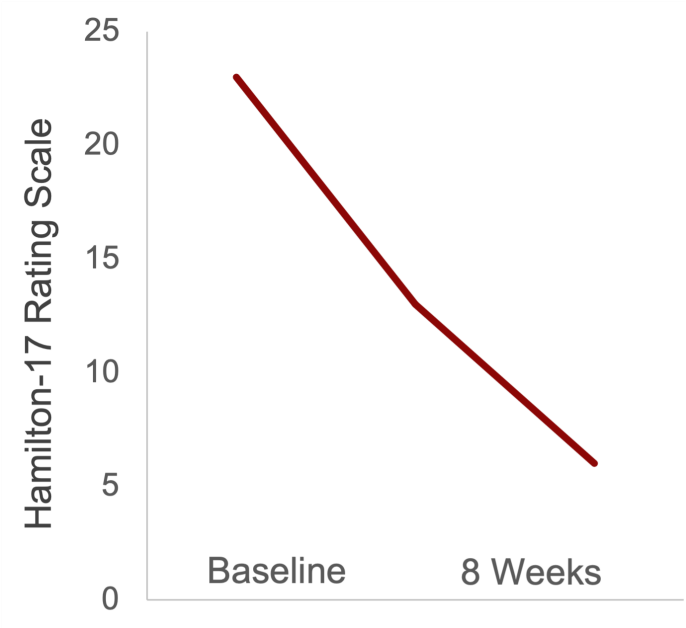
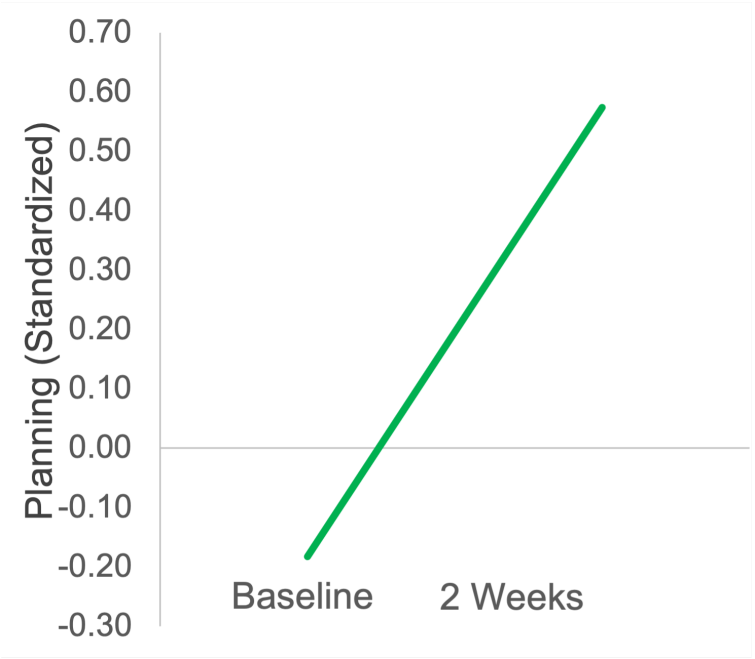
After 8 weeks of Guanfacine

Depression Score



Cognitive function



→ Had the motivation to return to work during pandemic and able to focus on projects; started planning vacation

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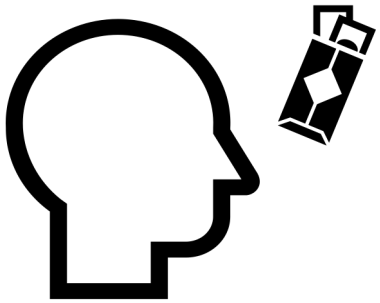
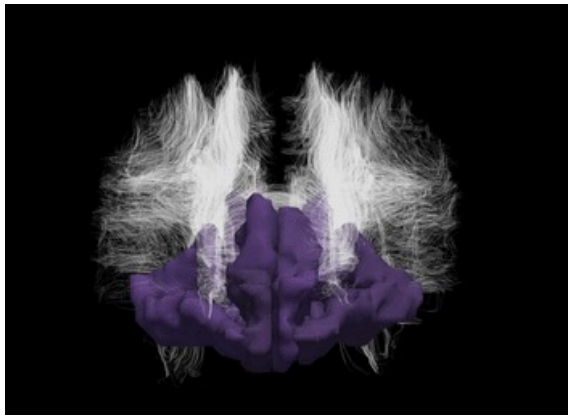
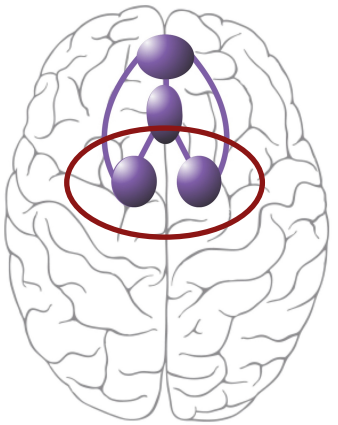


Reward dysfunction
Loss of pleasure
Loss of motivation



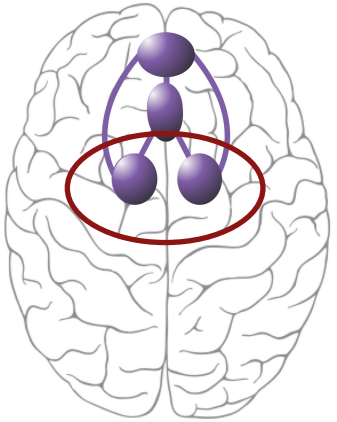
Positive affect
reward circuit



Ventral striatum

Targeting reward circuit and anhedonia with pramipexole

- Pramipexole is selective for D3 dopamine receptors
- D3 receptors are densely localized in the ventral striatum
- Pramipexole has been shown to increase ventral striatal activation
- Meets safety/availability criteria



e.g., Piercey et al. Neurosci Lett (1996); Camacho-Ochoa et al. Neurosci Lett (1995); Mierau et al. Eur J Pharmacol (1995); Kvernmo et al. Clin Ther (2006); Ye et al., Hum Brain Mapp (2011); Whitton et al. Brain (2020); Cusin et al. J Clin Psychiatry (2013); Corrigan et al. Depress Anxiety (2000).

Pramipexole: Moe's Case

- 37 years
- Deep depression with high level of anhedonia
- He had lost his job, was no longer engaging in activities that he previously enjoyed and began to isolate himself

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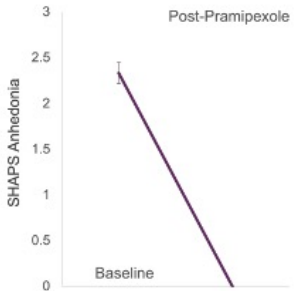
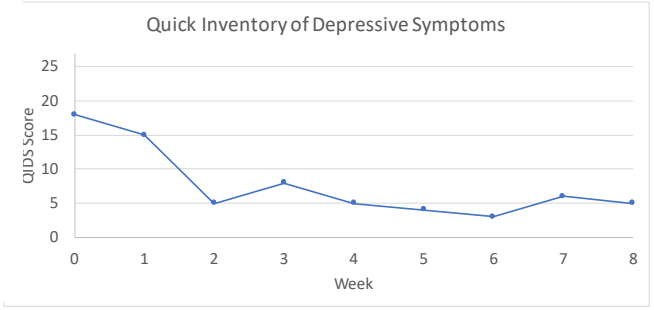
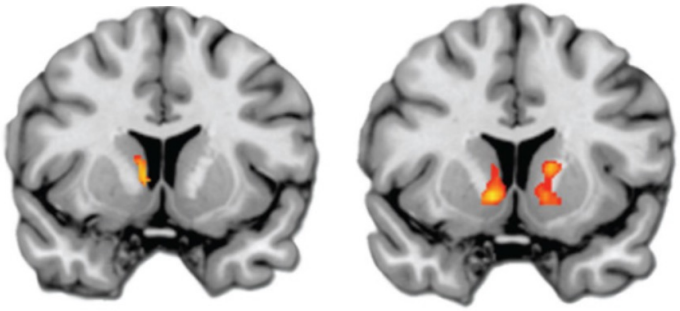
Pramipexole: Moe's Case

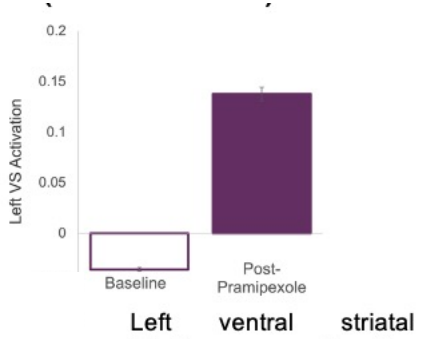
"The color has come back into my life…
I enjoy music and food again."

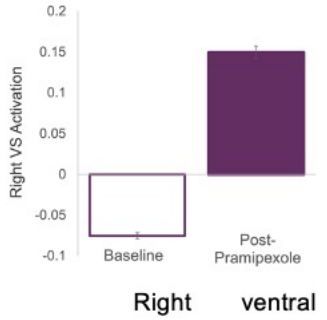




Suicidal thoughts resolved







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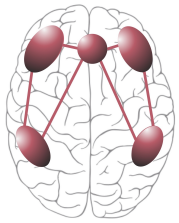
Biomarker Guided (BIG) Study of Depression

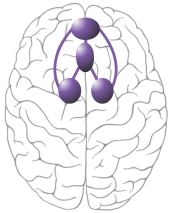
Subjects

Randomize

Outcomes



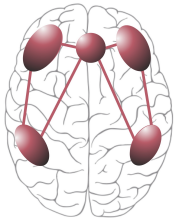
or



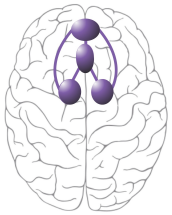
\+ anhedonia

\+ cognitive deficits

Pramipexole or Guanfacine



or



\+ anhedonia

\+ cognitive deficits

Pramipexole or Guanfacine

Quality of Life

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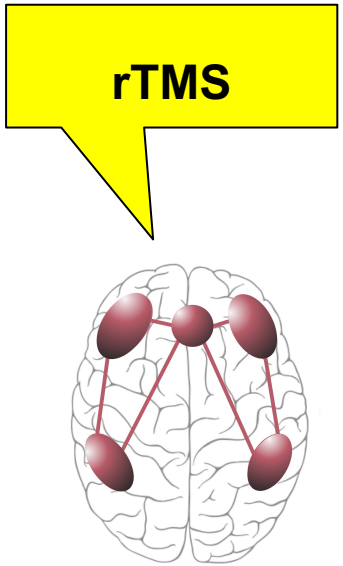
Mechanistic trials

Targeting cognitive control circuit with with neuromodulation techniques



Palo Alto
Providence
Dartmouth
Minnesota

Williams et al. BMC Psychiatry (2021)

NIMH. R01MH120126-01

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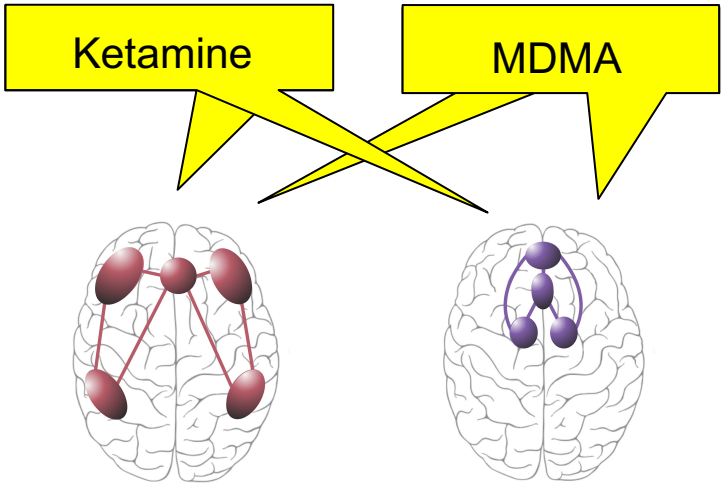
Probing the circuits with experimental drugs to understand the mechanisms by which they alter brain states









NIDA P50 Neural Circuit Dynamics of Drug Action: DA042012
Overall PIs: Karl Deisseroth and Lisa Giocomo ; Human Subjects PI, Williams
doi: https://doi.org/10.1101/2021.09.20.460992

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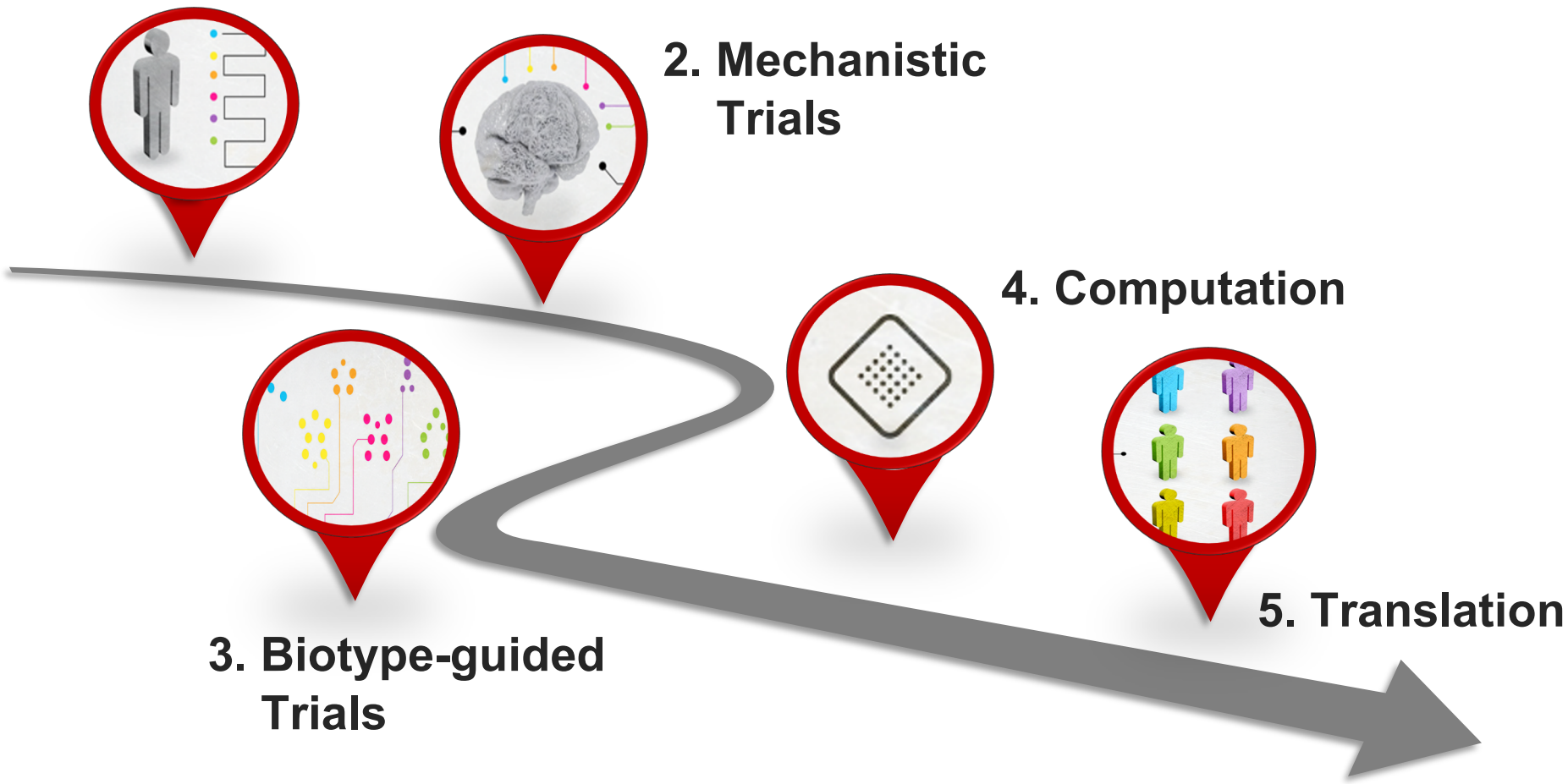
Our roadmap for precision mental health



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Thank you!

Research projects: *med.stanford.edu/pmhw*
Contact: *pmhw_admin@stanford.edu*

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